COMMENTS ON *CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION* EXPERT PANEL DRAFT REPORT ON THE REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF ACRYLAMIDE, MARCH 15, 2004

I. INTRODUCTION AND SUMMARY

On February 20, 2004, the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (CERHR) announced in the *Federal Register* (69 FR 7977) the availability of the draft Expert Panel Report on the potential reproductive and/or developmental toxicity associated with exposure to acrylamide. The report will be reviewed at an expert panel meeting, scheduled for May 17-19, 2004, for purposes of reaching "conclusions regarding whether exposure to acrylamide is a hazard to human development or reproduction." The expert panel is also charged with identifying any critical knowledge gaps and data needs to help establish research and testing priorities.

The following comments are submitted on behalf of the North American Polyelectrolyte Producers Association (NAPPA). NAPPA[1] represents the major manufacturers and importers of synthetically produced coagulants and flocculants, which are generically referred to as polyelectrolytes. A major class of these polyelectrolytes is polyacrylamides. Some of NAPPA's members not only produce these polyacrylamides, but they are also manufactures of the acrylamide monomer. For this reason, NAPPA members have a unique interest in this activity.

As described more fully below, NAPPA believes that it is critically important that the CERHR report clearly focus on the mechanism by which reported reproductive and developmental effects are expressed in the different animal species tested; the dose levels that are responsible for any reported reproductive and developmental effects; and most importantly, the significantly lower

[1] Members of NAPPA include: Ciba Specialty Chemicals, Degussa Corporation, GE Betz, Kemira Chemicals, Nalco Chemical Company and SNF, Inc.

exposure levels experienced by people from occupational, ambient environmental levels, the use of consumer products or food ingestion.

A review of the available studies show:

- The NOAELs for reproductive effects in rodents are an order of magnitude higher than those for neurotoxicity.
- Developmental effects are a result of neurotoxicity in the dams.
- The only reproductive effect observed in rodents is a decrease in litter size, which is due to dominant lethal mutations caused by glycidamide.
- Since humans produce significantly less glycidamide than rats and mice, humans would be expected to be substantially less sensitive to acrylamide-induced reproductive effects than rats and mice.
- The worst-case margin of exposure for humans (occupational) is at least 2,000. This value will be increased by at least approximately a factor of 4 due to the lower flux of acrylamide through the glycidamide pathway in humans as compared to rodents.

Based on the above, the CERHR should conclude that acrylamide does not present a reproductive risk to human health.

II. GENERAL COMMENTS

While the draft acrylamide assessment contains much of the critical literature on acrylamide, there are several important studies and references that are not included. Additionally, including a description of how the literature search was conducted would enhance the report and the criteria used for determining when to rely on primary *vs.* secondary sources. For example, the EU Risk Assessment on acrylamide was the sole source for the *in vitro* and *in vivo* somatic cell genetic toxicity results. Although it was released in 2002, the last literature search conducted by the EU was performed in 1995. As a result, the CERHR report ignores the *in vivo* rodent somatic cell studies performed between 1995 and 2003.

NAPPA recommends that in revising the report, the CERHR consider all of the recent studies/reports on acrylamide. Of particular note is a fairly recent article by Tyl and Friedman (2003),[2] which examined the effects of acrylamide on rodent reproductive performance. This article provides significant insight into the mechanism for the male reproductive effects, which allows an understanding of how to interpret the results with regard to cross species extrapolation. It is clear that at low doses, the male reproductive effects are a result of dominant lethal mutations while at higher doses, neurological impairment of either male or female becomes a factor.

CERHR is also encouraged to consider the recent review of polyacrylamides by the Cosmetic Ingredient Review (http://www.cir-safety.org/) as it provides more recent information than other secondary sources.

The document would be further enhanced by more clearly separating the discussion of rats and mice. These species respond to acrylamide differently in regard to metabolism and kinetics. For each reproduction or developmental study, comparisons are made to toxicity to the parental generation. While the reproductive physiology of these 2 species may be similar, the neurotoxicity of acrylamide is different with the rat being substantially more sensitive than the mouse. This difference should be highlighted in the background (Section 2) and carried forth through Sections 3, 4 and 5. In Sections 3, 4, and 5, rats and mice should be handled separately and then combined in the end.

Similarly, route of administration is a variable that should be separately addressed. Animals are exposed *ip*, *iv*, *po*, and in drinking water or diet. There are data in the literature on the impact of these routes of administration on the kinetic parameters that should be considered.

There is no indication in the report to indicate how the *in vitro* and *in vivo* somatic cell genetic toxicity test data will be used in the overall evaluation of the genetic or reproductive hazards of

[2] Tyl and Friedman, 2003. Effects of acrylamide on rodent reproductive performance. Reprod. Toxicol 17:1-13.

acrylamide. The relevance of the *in vitro* data is questionable, as in the accompanying BMD analysis, there is a sharp difference in the BMD for germ cells and somatic cells. On the contrary, the *in vivo* germ cell studies are important and these should be reviewed from the original articles, rather than secondary literature.

Attached is a report from Environ International that presents calculated BMDs for reproductive endpoints. As noted, failure to consider species and route of administration complicates the interpretation of the BMD and makes its use and relevance questionable.

Also, failure to consider the toxicity of acrylamide to the dams and in some cases to the males, is a weakness which permeates this document. For example, many studies are conducted at or near the LD_{50} with associated mortality. Neurotoxicity, which impedes mating, is a major consideration on evaluation of reproductive performance. Reference 124 deals with a quantitative attempt to investigate this parameter.

Inclusion of the funding source is incomplete. It is not clear why this is done. If it is important, then an effort should be made to make it complete. More important than funding source is GLP compliance. This should be stated for every study analyzed.

III. SPECIFIC COMMENTS

A. Section 1 – Chemical, Use And Human Exposure

1.2.1 Production Information

The draft report does not identify all of the current manufacturers of commercial acrylamide. There are four manufacturers of acrylamide in the United States: Ciba Specialty Chemicals Corp., Cytec Industries Inc., Nalco Chemical Co., and Flocryl, Inc. (part of SNF, Inc.). Given various mergers, acquisitions and name changes, NAPPA suggests removing company names that are no longer producing acrylamide.

Page 3 Lines 21-32; 1.2.3 Occurrence

There are several recent studies that address the occurrence of acrylamide in food that should be included. NAPPA suggests that, in addition to citing results from the Swedish studies and the efforts of FAO/WHO, CERHR also consider incorporating recent efforts by the Food and Drug Administration (FDA). In March 2004, FDA released its "Action Plan" for acrylamide in food.[3] The action plan outlines FDA's goals and planned activities on the issue of acrylamide in food and includes a timeline of major activities on acrylamide. In addition, in March 2004, FDA released new data on acrylamide levels in more than 750 new food samples.[4] These data expand the available information on the presence of acrylamide in the food supply. While most of the results are similar to those previously reported from Europe, FDA also found acrylamide present in products heretofore not previously identified including black olives, prune juice and Postum, a powdered beverage.

Page 5 Lines 17-22; 1.2.3 Occurrence

The draft CERHR report should be revised to clarify the statements suggesting that exposure to acrylamide may result from plant site releases into the environment and from the leaching of acrylamide from the use of polyacrylamide polymers.

The draft states that, according to the Toxic Release Inventory (TRI), 8.7 million pounds of acrylamide were released to the environment in 2000. A closer examination of the TRI data reveals that the overwhelming majority of the acrylamide reported as being "released" to the environment, was in fact disposed of via underground injection.

Underground injection is a method by which fluid wastes are disposed of into deep geological layers of the earth. It is a proven, safe technology that is regulated by the Environmental Protection Program (EPA) in accordance with Underground Injection Control (UIC) program. According to the EPA, potential risks from injection wells are extremely low because wastes are

[3] http://www.cfsan.fda.gov/~dms/acrypla3.html
[4] http://www.cfsan.fda.gov/~dms/acrydat2.html

permanently disposed of into saline aquifers far below any usable water supplies. While these values are reported to the TRI, they should not be considered releases to the environment.

EPA recently made available the TRI results for 2001. The 2001 TRI data indicates that 19,394 pounds of acrylamide can be classified as released to the environment as follows:

Air	:	10,219 pounds
Water	:	140 pounds
Land	:	9,035 pounds

Additionally, the 2001 TRI results also show that over 7,500,000 pounds were disposed of through the UIC regulated program and 11,411 pounds are categorized as Total Off-Site Releases. For the reasons described above, these values should not be included in the estimates of release to the environment.

The discussion regarding the leaching of acrylamide monomer from polyacrylamide products should be revised. Human exposure to acrylamide through its migration in the environment is insignificant. Acrylamide is inherently unstable in the natural environment. Degradation, both biotic and abiotic, has been shown to be rapid. The residual acrylamide in polyacrylamide used in sludge dewatering processes is not discharged with the treated water but is recirculated with the filtrate to the primary clarification where it is rapidly biodegraded. Acrylamide is hydrophilic/lipophobic. It has a negative log P_{ow} and does not bioaccumulate.

1.2.4.1 General Population Exposure

NAPPA concurs with the CERHR's evaluation that industrial releases of acrylamide to surface waters are limited and unlikely to accumulate because of biodegradation. Further, because acrylamide is highly water soluble and not lipophilic, it will not bioaccumulate.

The report overstates the extent of human exposure from the use of various consumer products including cosmetics. The draft principally relies on the European Union risk assessment for purposes of estimating dermal exposure through contact with consumer products. To assess

potential human exposure, the EU used a worse case assumption of 75% dermal absorption. Since the issuance of the EU report, additional studies have been conducted which document that actual absorption in people is significantly less, and is likely less than 5%.

For various reasons, the use of the Sweden tunnel incident for calculating a worst-case exposure estimate of drinking water contamination is inappropriate and should be removed from the report. First, the tunnel incident did not involve an acrylamide-based grout; rather, the product was based on *n*-methylolacrylamide (NMA) and contained only residual acrylamide. This product was not properly applied in the tunnel and therefore represents a case of "misuse." More importantly, studies of people involved in the tunnel incident did not identify any reproductive or developmental effects associated with exposure.

It is also relevant to note that the CERHR's statement that the use of acrylamide grout has been phased out is incorrect. In fact, on December 2, 2002, the U.S. Environmental Protection Agency (see 67 FR 71524) concluded its Toxic Substances Control Act rulemaking activities regarding the use of acrylamide and NMA based grouts. The Agency decided that there was no need to impose any restrictions on their continued use since "EPA has determined that as long as appropriate PPE is used during grouting operations, it is no longer necessary to prohibit the use of these grouts to protect the health of grouters."

1.2.4.2 Occupational Exposures

NAPPA believes that the draft report does not appropriately characterize the availability of data on occupational exposure. It concludes that "exposure data are inadequate for estimating current exposures," this despite the fact that there is an extensive discussion of occupational exposure studies and a series of tables summarizing occupational exposure data.

While the draft report cites some of the occupational exposure data from the European Union risk assessment report, it fails to acknowledge, which the EU did, that "extensive air sampling has been carried out by industry" and which forms the basis of the occupational exposure section. Since operations in the U.S. are relatively similar to Europe, CERHR should have relied more extensively on the EU results. It is relevant to note that the major difference between

European and U.S. operations is that there are no longer any U.S. facilitates manufacturing solid grade acrylamide and hence exposures during monomer operations are considerably less than that reported in the EU assessment.

The highest occupational exposures are encountered during the manufacture of acrylamide-based polymers (polyacrylamides). The exposure levels, however, are all situated below the OSHA PEL of 0.3 mg/m^3 in the air (0.04 mg/kg/day). In several cases the air concentrations are kept below the ACGIH recommended OEL of 0.03 mg/m^3 in the air (0.004 mg/kg/day). In all manufacturing sites, the real exposures are substantially lower than the regulated OEL. Furthermore, absorption of acrylamide through the inhalation route has been shown to be less than 50% in rats. Therefore, the highest occupational exposure to acrylamide through inhalation is less than 0.002 mg/kg/day. In most cases, due to good industrial hygiene practices, this will be between 2 and 10 times lower.

In the case of dermal exposure, absorption of acrylamide through this route as determined in human volunteers is approximately 5% over 24 hours and current personal protection is very effective (breakthrough time greater than 24 hours). The use of 50% solution has resulted in almost no dermal contact with acrylamide monomer in the manufacturing sector.

Other occupational exposures are significantly lower than polymer manufacturing. Polymer use in waste water treatment and coal preparation are insignificant due to the very low exposure times involved and low level of residual monomer in polymer. A study performed by Virginia Commonwealth University and confirmed by NIOSH demonstrated that sewer grouting results in practically no exposure to acrylamide when liquid-grade acrylamide is used.

B. Biological Effects

Location	Comments and Corrections
Page 16, Line 47	There is no way complete absorption of acrylamide from the GI tract could be demonstrated from an *i.v.* study. There is no data on the complete absorption of acrylamide from the GI tract in rats.

Location	Comments and Corrections
Page 17, Line 1	The use of secondary sources here, belays the importance of the Sumner *et al.* article (reference 40). In this study, researchers directly compared the dermal, *p.o.*, and inhalation absorption of acrylamide as well as characterized the distribution, ratio of acrylamide to glycidamide hemoglobin adducts. The use of the Barber *et al.* study (reference 41) in the strengths/weaknesses section is poor, as analysis of these results shows the cysteine moieties in hemoglobin are rapidly adducted, saturated and not relevant. The most current review on this subject was conducted by CIR in 2003. The authors should review the Sumner paper more carefully as applies to this section. As far as absorption and dose are concerned, there is a study in humans that has been submitted for publication and a draft of the manuscript or a copy of the final lab report can be made available to the committee. This work shows remarkable consistency among human volunteers.
Page 20, Line 8	The use of placentas is misleading for the issue of fetal absorption. The work of Marlowe *et al.* using autoradiography in pregnant female mice, showed that virtually no acrylamide passed into the fetus of mice on day 13.5 but the placenta became freely permeable by day 17.5. The day 17.5 aspect of the Marlowe study is analogous to the human placentas studied by Sorgel, but not reflective of fetal exposure during development.
Page 29, Line 17	The positive responses in the cell transformation tests should not be considered evidence of genetic toxicity because these are not genetic toxicity tests. They are more properly included in the section on carcinogenicity.

Location	Comments and Corrections
Page 30, Line 5	The positive responses in the cell transformation tests should not be considered evidence of genetic toxicity because these are not genetic toxicity tests. They are more properly included in the section on carcinogenicity.
Page 37, Line 21	The wording of this sentence is misleading; the male germ cell data do not indicate that spermatogonia may be the most sensitive stage. In fact, the data indicate that the spermatogonia may be the least sensitive stage.
Page 37, Lines 25-26	Suggest adding "weeks 1-3 postexposure" to the sensitive stages of spermatogenesis.
Page 42, Table 9	The positive responses in the cell transformation tests should not be considered evidence of genetic toxicity because these are not genetic toxicity tests. They are more properly included in the section on carcinogenicity.
Page 48, Lines 5-29	The parenthetical comment regarding the dominant lethal test is confusing and a bit muddled.
Page 48, Line 31	The role of glycidamide in the induction of dominant lethal effects is not addressed in §2.3.2.6, as noted.
Page 59, Line 2	The review of the Pacchierotti *et al.* study concludes that results from the *i.p.* dosing route may not be relevant to humans or for the evaluation of human risk. This disclaimer is not included in the conclusions of the other *i.p.* sperm cell studies. This is true of most of the genetic toxicology literature.

Location	Comments and Corrections
Page 61, Lines 17-19	Suggest carrying the questions to Chapter 5.0 (Summary, Conclusions and Critical Data Needs, p. 149ff) on whether the protamine (chromosomal proteins) or DNA adducts are causal for the genetic toxicity, and whether the neurotoxicity has a different mechanism than the genetic/developmental/ reproductive toxicity effects.
Page 70, Section 2.3.2.6	The mammalian spot test is an *in utero* somatic cell test and should not be included with the germ cell tests.
Page 72, Figure 4	Figure 4 and its legend are not very clear, the legend is incomplete, and the dominant lethal data do not appear to be plotted correctly.
Page 77, Line 29	The CERHR needs to consider new studies by Erdreich (2004) and Mucci (2004).
Page 79, Table 13	The report does not reference the Damjanov and Friedman (1998) reread of the mesothelioma data where he concludes that these tumors were not malignant. (Mesotheliomas of the Tunica Vaginalis Testis of Fischer 344 (F344) Rats Treated with Acrylamide. In Vivo 12:495-502.) In the Johnson study there was no significant increase in malignant tumors. The malignant tumors only become significant when combined with benign which are generally significant, anyway. No discussion was made of the Johnson study exceeding the MTD, the substantial viral infection which occurred during the study, or the failure of tumors incidence to exceed historical background. No conclusion was made that the Friedman study was better conducted and should be used.
Page 83, Section on GST	GST is involved in metabolism of glycidamide while acrylamide appears to react directly with GSH. There appears to be little or no glycidamide GST in humans so this discussion is mute.

Location	Comments and Corrections
Page 86, Line 2	This discussion will be changed by the results of human studies. See CIR Monograph for review of these studies. Manuscript is in preparation. A draft can be provided if it is useful.
Page 86, Line 9	Singling out cysteine reactivity is not helpful. Acrylamide and glycidamide participate in a variety of chemical reactions with proteins. What is helpful is to discuss the N-terminal valine adduct which is a biomarker of acrylamide exposure.
Page 86, Line 12	Reference to JIFSAN is an extreme secondary reference. Need a reference to Gamboa da Costa G *et al.* (2003 DNA adduct formation from acrylamide via conversion to glycidamide in adult and neonatal mice. Chem Res Toxicol. Oct;16(10):1328-37.)
Page 86, Line 15	The reaction of acrylamide with GSH is not enzymatic. None of the references show enzymatic reaction. Glycidamide conjugation is primarily enzymatic, and as was said earlier, the enzyme does not exist in humans.
Page 86, Line 27	This was not discussed in this section and should be.
Page 91, Line 26	Math does not work out. 12 gms/rat/day of 400 ppm acrylamide = 4.8 mg/rat/day. For a 300 gram rat, the dose is 4.8/0.3=16 mg/kg/day not 1.4 as stated in the text. We hope this is not an endemic problem as this is the only measurement where all the assumptions are transparent. ***This is critical as dosimetry appears to be based on these calculations***
Page 102, Line 9	Fischer 344 rats are notoriously poor candidates for study of reproduction. That the females had no body weight changes at 20 mg/kg is inconsistent with other data in this report.
Page 103, Lines 49-50	See general comments for clarification. The number of animals evaluated on pnd 24, 58, 59, or 60 should be indicated.

Location	Comments and Corrections
Page 104, Line 37	Identification of use of EPA Guidelines as a weakness is incongruent with toxicology testing. Clearly well defined and validated protocols are the heart of toxicological validation. The sentence should be removed.
Page 106, Line 2	This study is an *in vitro* study evaluating properties which do not appear effected *in vivo*. Consideration of this study should be either removed or moved to the section on neurotoxicity.
Page 106, Line 50	Mortality of 10% of the test population should raise questions about interpretation of the remaining results. Instead a BMD is calculated. This study should be moved to the genetic toxicology section and the BMD calculations removed.
Page 108, Line 39	Please indicate route of administration if Nagao provided it.
Page 110, Lines 6-9	Consider adding: "The Friedman *et al.* study was specifically designed to experimentally examine a statement by Hussein in his paper, which the EPA interpreted as indicating progressive offspring hindlimb weakness."
Pages 110-111, Lines 41-5	Consider adding: "The postwean weight gain curves for the control and treated group males were parallel, *i.e.*, weight gains as percentages of initial and subsequent body weights were the same, with no evidence of postwean neurotoxicity."

Location	Comments and Corrections
Page 114, Line 21	The conclusions referred to here suffer from the problems identified in the introductory section. First, rats and mice are mixed and confused. The metabolism and kinetics of acrylamide are very different in these animals. Secondly, acrylamide is highly neurotoxic in all of these developmental studies. The appropriate conclusion occurs in line 12 rather than up front. That is based on current data, "The Expert Panel was unable to separate the effects of acrylamide on rat or mouse offspring from effects that may have been due to maternal toxicity. The Expert Panel concludes that acrylamide treatment of male mice prior to mating can result in developmental toxicity manifested as abnormal preimplantation embryos." With regard to effects in males, the conclusions drawn by Tyl and Friedman still appear to apply. The male mediated effects are a result of dominant lethal mutations at low doses and neurotoxicity at high doses.
Page 116, Line 17	Suggest "…or whether only pregnant animals…" if that is what the text means.
Page 117, Line 15	The impact of the 100 ppm dose on water and food intake (see reference 124) and neurotoxicity may be a contributing factor to evaluating these findings. Interpreting this maternal toxicity as a developmental response is highly misleading.

Location	Comments and Corrections
Page 118, Lines 41-49	The authors stated that phenobarbital (PB) co-treatment with acrylamide prevented "both neurotoxicity and decreased relative testicular weight." Since they apparently did not perform histopathologic examination of the testes in the co-treatment group, and only relative testis weight was affected, what are the body weights in this group? If PB accelerated metabolism of everything, then it might be expected that body weights were reduced, which would increase relative testis weight versus an animal with a greater body weight, with the same testis weight. Of course, phenobarbital effects on hormone metabolism might also be a contributing factor in these studies.
Page 121, Lines 27-28	This statement implies that only anaphase segregation of chromosomes during mitosis of gonial cells is affected. What about anaphase segregation of chromosomes during Meiosis I and/or II?
Page 122, Lines 17-18	The statement by the study authors "that glycidamide is involved with reproductive toxicity but not neurotoxicity associated with acrylamide exposure," is a very important statement but does not appear to be supported by the study described or to be consistent with the results and interpretation of other studies. This needs to be brought forward.
Page 124, Lines 9-30	This discussion on reduced acrylamide-induced dominant lethality after phenobarbital pre-administration is, in fact, contradictory to the body of data indicating that acrylamide is not metabolized to an inactive metabolite, and that glycidamide is active and may, in fact, be responsible for reproductive toxicity. The role of acrylamide metabolism in dominant lethality has been investigated in reference 77. Furthermore the enzyme responsible for acrylamide metabolism was elucidated in reference 49.

Location	Comments and Corrections
Page 128, Line 17	The use of ovarectomized females which were hormone stimulated represents a novel technique for isolating and monitoring effects on male rats. Reference to strengths and weaknesses should include comment on the unusual protocol used in this study.
Page 131, Lines 28-30	In Tyl *et al.* (2000), statistically significant pairwise effects were observed at 45 and 60 mg/kg/day, but the authors (and the CERHR; see Figure 8, page 134) noted that there was a clear decreasing trend for the number of implants/female and a clear increasing trend for % postimplantation loss/litter. Statistical analyses are a tool, tempered by biological relevance and experience.
Page 131, Lines 44-45	The evaluations for neurotoxicity were limited to daily clinical observations and grip strength just prior to necropsy for the treated males. Reduced weight gain/increased weight loss from food deprivation may be (most likely is) very different from the same findings in acrylamide-treated males, both in terms of causation and consequences. The authors consider the weight changes as indicative of and consistent with systemic toxicity at 15 to 30 mg/kg/day, with likely subtle neurotoxicity at least contributing to the observed reproductive toxicity.

Location	Comments and Corrections
Pages 131-132, Lines 50-3	The study authors stated that the decreased mating index and reduced fertility are not likely due to clastogenicity during spermatogenesis (since the sperm were in the epididymis at the time of acrylamide exposure, with their DNA compacted and "coated" with protamines). These findings were considered more likely due to male hindlimb foot splay (which could interfere with mounting) and possible penile nerve effects (which could impact on penile penetration and cervical stimulation), as well as effects on the flagellar motor proteins (which could impact on sperm transit from cervix to uterus). This interpretation is consistent with normal numbers of vaginal sperm but reduced uterine sperm observed by Sublet *et al.* (1989).
Page 134, Second Paragraph	Use of post implantation loss represents a linked variable and its relevance under conditions where neither of the parameters which go into calculating it have changed is questionable. See the included EnvironCorp report for a discussion of this finding. Furthermore, since studies have been replicated in this report, it would be highly valuable to summarize across studies to calculate BMDs.
Page 143, Lines 33-34	"Full litter loss" is usually ascribed to maternal reproductive toxicity and not to developmental toxicity (the opposite of the CERHR view). The view that it is the dam's "problem" is supported by data from the EPA on full litter losses in rats from exposure to certain disinfection by-products (DBPs), traced to problems in serum LH levels early in the pregnancy, necessary for maintenance of the pregnancy.
Page 143, Line 34	"Decreased pup weight" may also be due to maternal toxicity, impacting fetal/pup growth, although it is correctly termed "developmental toxicity."

Location	Comments and Corrections
Page 146, Lines 8-10	The text reads "There were dose-related decreases in the number of fetuses/dam that were pregnant, resorptions per dam, and offspring per dam." In fact, there were decreases in the number of fetuses and offspring per dam, but the numbers of resorptions per dam were increased, as one would expect to result in reduced fetuses and offspring.
Page 147, Boxed text	This reviewer does not think that it is coincidence that "malsegregation of chromosomes" is controlled by the mitotic/meiotic spindle fibers which contain the motor protein kinesin, that sperm motility is due to the motor proteins (*i.e.*, kinesin) in the flagellum, and that axonal flow of nutrients, etc., is dependent on motor proteins in the axon, and that acrylamide and/or glycidamide forms adducts with proteins (including the motor proteins and the protamines in the chromatin complex).

General/Minor Corrections/Suggestions

Location	Corrections
Page 29, Line 21	"malsegregation" (correct spelling)
Page 35, Table 10	"chromosomal aberration**,** aneuploidy,…" (add comma)
Page 58, Table 12; Page 102, Line 9; Page 103, Line 10; Page 137, Line 29; Page 146, Line 42	"Fis**c**her" 344 rat (correct spelling)
Page 74, Line 47	"presumably" (remove "e")

Location	Corrections
Page 69, Line 13; Page 127, Line 42; Page 131, Lines 5-6; Page 138, Lines 22, 49	The statistical test is correctly termed "Fisher's exact test"
Page 93, Line 36	"gluc**u**ronidase" (correct spelling)
Page 94, Table 18, first footnote	"…raising treated pup**s**" (make "pup" plural)
Page 96, Line 16	"…**after** a single injection" (change "about" to "after")
Page 97, Lines 50-51	"…acrylamide **at** 0, 205…" and "acrylamide **at** 0, 3…" (add "at")
Page 101, Figure 5	Add "mating" to "time of treatment after" on abscissa of upper graph.
Page 103, Lines 49-50	"Animals naive to the test were evaluated on PND 24 and one of PNDs 58-60…" What does "one" refer to? One of the PNDs or how many animals were evaluated?
Page 120, Lines 11-12	"Two tubule segments at Stage I were planned from each testis…" Does the review mean "planed" or something else?
Page 135, Line 40	"suspect" (close quotation)
Page 138, Line 12	"Mann-Whitney U" (not "Mann-Whitne**u** U")
Page 141, Table 31	"Pup weight female?" (delete the question mark)